REMARKS

Applicants thank the examiner for his comment regarding improper status identifiers and have made the noted corrections.

In the Office Action mailed September 21, 2005:

Claims 11, 48, 49, 50 and 58 were indicated to be allowable.

Claims 1-8, 10, 12, 25-27, 31, 34, 36-37, and 60 were rejected under 35 U.S.C. 103(a) as anticipated by Frazier et al.(WO 01/93930) in view of Pisano et al. (US 5,928,207).

Claims 9, 13-15, 18,19 and 21-24 were rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al., as applied to claims 1-8, 10, 12, 25-27, 31, 34, 36-37 and 60 above, further in view of Say et al.(US 6,134,461).

Claims 16 and 17 were rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Say et al, as applied to claims 9,13-15, 18, 19 and 21-24 above, further in view of Meade et al. (US 5,770,369)

Claim 20 was rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Say et al., as applied to claims 9,13-15, 18, 19 and 21-24, further in view of Lin et al.

Claim 57 and 61-66 were rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Lin et al.

AMENDMENTS TO THE SPECIFICATION

The specification has been amended to correct a mislabeling in the table of drawing reference numbers.

CLAIM AMENDMENTS AND ADDITIONS

Claims 61-63 and 66 have been cancelled without prejudice. The applicants reserve the right to pursue the subject matter of the cancelled claims in a later filed continuation application.

Claim 1 has been amended to recite that the microprobe device is absent a closed fluid channel in any portion of the device that penetrates into the subject. Support for this limitation can be found in the specification e.g., as appears at page 13, lines 7-13 (see paragraphs 0097 in the published version of the application, US Patent Publication 2002/0137998). The absence of a

closed channel, i.e. the absence of an internal bore, is specifically disclosed and the advantages of such absence taught. None of the figures in the application shows such a closed fluid channel. At page 13, lines 7-11, an open fluid channel is explicitly disclosed, and FIG. 2C clearly shows it as groove 26G in a portion of the microprobe device that penetrates into the subject (microprobe 26). At page 5, lines 23-28 (paragraph 0016 in US Patent Publication 2002/0137998) an ex vivo portion of the microprobe device that does not come into direct contact with the analyte tissue is disclosed. There is, therefore, a corresponding in vivo portion of the device, including the in vivo probe tip, that penetrates into the subject to contact the analyte tissue. The combination of these disclosures is equivalent to teaching " the microprobe device being absent a closed fluid channel in any portion of the device that penetrates into the subject". As such, the applicants submit that no new matter has been entered with this amendment.

Claim 57 has been amended to depend from claim 1, and claim 64 amended to depend from claim 57. Claims 57, 64 and 65 have been amended to remove the word "substantially", and to recite that the entire area of the tip and of an adjacent portion of the penetration end extending at least 50% of the distance from the tip to the body end of the microprobe portion has a uniform thickness. Support for this modification can be found in FIG. 3B, where the entire microprobe portion is of uniform thickness. The applicants submit that the term "uniform thickness" allows for some acceptable degree of unintended variation from perfect uniformity, e.g., due to limitations of the process used to fabricate the microprobe portion. Claim 65 has also been amended to add the limitation that the body portion retains the initial thickness of the silicon substrate. Support for this limitation can be found in the specification at page 11, lines 14-17 (paragraphs 0095 in the published version of the application, US Patent Publication 2002/0137998). As such, the applicants submit that no new matter has been entered with this amendment.

NEW CLAIMS

Claim 67 has been added to provide a desired range of coverage, namely that the substrate from which the microprobe device may be formed is silicon, rather than single-crystal silicon. Support for the claim is found throughout the specification and in the description of the silicon substrate in claim 11.

Claim 68 has been added to provide a desired range of coverage. As discussed in the specification, features of embodiments shown in various figures may be employed in

combination with embodiments shown in other figures (page 20, lines 10-12). A cover, a feature which is disclosed in the Transmitter Embodiment is useful with all embodiments of the microprobe. At page 17, line 1, page 18, lines 3-40, applicants disclose that the body portion of the microprobe device may be sealed with a cover. The portion of the microprobe device that penetrates into the subject is left uncovered so that the microprobe can access the analyte-containing fluid (page 17, lines 13-14, FIG. 5B).

Claim 69 has been added to eliminate a biosensor microprobe device with a channel which has an axial opening in the direction of the penetration end such that the opening is aligned with the apex of the microprobe. No channel opening of this type, which could weaken the microprobe, is disclosed in the in the specification or indicated in any of the figures.

Claim 70 has been added to require that the top surface of the silicon substrate of the microprobe device is planar, including the top surface perimeter of any channels, cavities, or holes recessed therein, but excluding the surface area within the perimeter of recessed portions. Support for this claim can be found in FIG. 1B, where the entire substrate is planar. The applicants submit that the term "planar" allows for some acceptable degree of unintended variation from perfect uniformity, e.g., due to limitations of the process used to fabricate the substrate.

Applicants submit that no new matter has been added with these new claims.

INTERVIEW SUMMARY

In a telephone interview with Attorney Joshua Isenberg and Agent Margaret Smart on December 16, 2005, the Examiner indicated that the above amendment wound not be entered unless a Request for Continued Examination was filed. The Examiner also indicated that the amendment to claim 1 would distinguish over the prior art of record.

CLAIM REJECTIONS

The Applicants submit that the rejections of claims 61-63 and 66 are moot in view of cancellation of these claims.

Claims 1-10, 12-27, 31, 34, 36-37 and 60

Claim 1was rejected under 35 U.S.C. 103(a) as anticipated by Frazier et al.(WO 01/93930) in view of Pisano et al. (US 5,928,207). Claim 1 has been amended to recite that applicants' biosensor microprobe device does not have a closed fluid channel in any portion of the device that penetrates into the subject. In conventional hollow metal needles, the internal bore is fabricated by drawing the steel over a mandrel. In hollow silicon microneedles, the internal bore is created by forming a closed channel in the silicon, This can be done either by forming side and top walls sealed over the top of a flat silicon substrate (Frazier, Lin), or by etching a depressed channel in a solid substrate and sealing a top over the channel (Pisano). Applicants' device is not a hollow microneedle; it is a solid microprobe formed by a single silicon substrate, without the internal bore which would be formed by a closed channel.

Frazier et al. disclose a microneedle device with a hollow elongated shaft defining a closed channel providing fluid communication from a proximal end to a tapered distal end (Abstract, page 31, lines 1-8). The shaft includes a bottom wall formed by a solid layer, and opposing sides walls connected by a top wall (page 7, lines 26-28 and Fig. 1B) which close the channel around its circumference. The closed fluid channel has small fluid inlet/outlet openings at the proximal and distal ends.

The hollow microneedle of Frazier et al. can be used for either fluid injection or extraction (Abstract), depending on the direction of flow through the channel. In operation, the microneedle is inserted through the skin, causing the distal end of the closed fluid channel to penetrate into the subject. Fluid injection requires that at least a portion of the closed channel penetrate into the subject in order to deliver the injectable fluid to its target. Similarly for fluid extraction, the closed channel must penetrate into the subject to permit pumping of the fluid through the channel over the in-channel biosensor, and out the proximal port. For a single analyte measurement, the closed channel shaft must penetrate to a depth that the biosensor is covered. Further, the placement of the biosensor within the needle channel provides the obvious advantage of protecting the sensor during penetration of the tough stratum corneum.

There is no motivation in the Frazier reference to remove the closed channel of the hollow microneedle. Such a change would expose the sensor and prevent device use for fluid injection or for extraction using the variety of pumping and transducer mechanisms disclosed (page 6, lines 29-32, page 7 lines 1-13). Frazier et al. therefore do not teach or suggest, and in fact teach away from, claim 1 as amended to recite a microprobe device" being absent a closed channel in any portion of the device that penetrates into the subject."

Pisano et al. disclose a single-crystal silicon hollow microneedle with a closed channel to transport fluid for either fluid injection or extraction, depending on the direction of flow through the channel. A pumping mechanism and a sensing element incorporated within the channel on the body of the device are also disclosed. Pisano et al. also disclose a single-crystal silicon lancet microprobe without channel or top cap but nowhere teach or suggest combining a sensing element or biosensor with the solid lancet microprobe. For this reason, and for the reasons discussed for Frazier et al. above, the combination of Frazier with Pisano et al. does not teach, and in fact teaches away from, a biosensor integrated into a microprobe device, the device" being absent a closed channel in any portion of the device that penetrates into the subject" as set forth in claim 1.

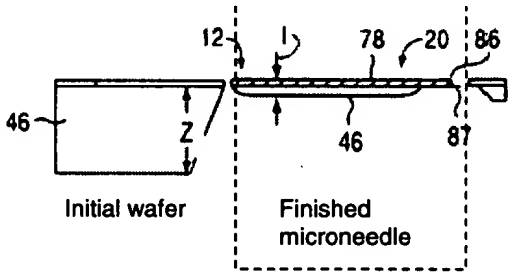
Hollow microneedle devices for use in analyte monitoring suffer from significant disadvantages in terms of MEMS fabrication complexity and cost. In the *in vivo* embodiment of Applicants' biosensor microprobe, the miniaturized biosensor comes into direct contact with the fluid to be analyzed when the microprobe punctures the skin (Fig. lA, paragraph 92). As a result, the biosensor microprobe can continuously measure changes in analyte concentration in the bulk fluid over time without the need for fluid transport. Microprobe construction is simpler and less expensive than that of a hollow microneedle because only a single silicon substrate is used The exact shape of a solid microprobe can be more readily optimized to permit reliable, painless skin penetration. No waste fluid is exuded via an exit port, thus avoiding any blood disposal problem. These advantages are achieved using fewer elements while retaining the same analyte monitoring functionality. No pumping mechanism, nor side and top walls, are required. This retention of function with fewer required elements provides a strong indicia of unobviousness.

Furthermore, claims 2, 5-10, 12, 26-27, 31, 34 and 37 depend from claim 1 and recite additional features therefor, claims 3-4 depend from claim 2, claims 13, 25 depend from claim12, claims 14, 16, 18 depend from claim13, claim 15 depends from claim14,claim 17 depends from claim16, claims 19-24 depend from claim18, claim 36 depends from claim 34, and claim 60

depends from claim 5. As such, and for the same reasons set forth above, the applicants submit that these dependent claims define an invention suitable for patent protection.

Claims 57

Claim 57 was rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Lin et al. Claim 57 has been amended to require a uniform thickness over the entire area of the tip and of an adjacent portion of the penetration end extending at least 50% of the distance from the tip towards the body end of the microprobe. As the Examiner has noted, Frazier et al's microneedle is tapered. Frazier et al. disclose (as discussed under claims 64-65 below) that the thickness of the bottom wall is typically about 10-20 micrometers thinning to less than 7 micrometers at the tip, a decrease in thickness of at least 30%. Frazier's microneedle therefore does not have a uniform thickness over the entire area as set forth in claim 57 as amended.



I = 50 micrometers
Z=500-550 micrometers
46 silicon substrate
12 proximal shank end
20 distal end

FIG 2B

A copy of FIG. 2B of Lin et al. is presented above for the Examiner's convenience. Note that the figure is not to scale in order to show the detail of the tip region. The figure shows a cross-sectional view of Lin's finished, detached microneedle. The entire single-crystal silicon wafer substrate 48 is thinned during fabrication, resulting in a uniform 50 micrometer thickness over the shank end (or body) (column 7, lines 40-43 and along the shaft (column 4, lines 22-24). However, Lin teaches that the tip region is etched further, removing single-crystal silicon 50 micrometers from the tip end (column 7, lines 45-48). Furthermore, it can be seen from FIG. 2B that the thickness of the shaft 50% of the distance from tip end is equal to the thickness of the shank (body) portion, i.e. 50 micrometers. Therefore Lin et al do not disclose a microneedle where the entire area of the tip and of an adjacent portion of the penetration end extending at

least 50% of the distance from the tip to the body end of the microneedle has a thickness that is less than the thickness of the body portion as is recited in claim 61 as amended.

Furthermore, it would not be obvious to modify Frazier to form a body portion that is thicker than the shaft portion of the microprobe. Frazier at al. teach a separate flange that can be attached to the microneedle at any desired point along its shaft in order to set the penetration depth and attach the microneedle to the subject penetrated. Frazier et al. also teach the use of the microneedle fitted with a syringe to inject fluid, in which case the flange is not desirable. A fixed, integrated body portion thicker than the shaft would not provide this flexibility. There is therefore nothing in Frazier et al. to suggest the desirability of a body portion thicker that the shaft.

Claims 64-65

Claims 64-65 were rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Lin et al. These claims recite limitations regarding the thickness of the tip of the microprobe portion of the silicon substrate into which the biosensor is integrated. Claims 64 and 65 have been amended to require a uniform thickness over the entire area of the tip and of an adjacent portion of the penetration end extending at least 50% of the distance from the tip towards the body end of the microprobe. Claim 64 has been further amended to remove the limitation that the portion of uniform thickness be less than the thickness of body. Claim 66 has been amended to recite this limitation. At pages 9-10, Frazier et al. provide dimensions for the following parameters: inside microchannel height and width, microneedle length, and width between sidewalls and center-to-center spacing for microneedle arrays. Frazier et al. are silent with respect to the thickness of the microneedle wall at its tip Typical bottom wall dimensions of about 10-20 micrometers (page 14, line 8) are disclosed, along with three specific examples of microneedle wall thicknesses of about 20 micrometers (Page 13, line 32, page 25 lines 11-12, page 26 line 1). However, Frazier et al.'s microneedles are tapered at their tip (page 6, line 19). At page 25, lines 28-29, outer tip dimensions of less than 15 x 15 square micrometers are disclosed, which would result in a bottom wall dimension at the tip of less than 7 micrometers, assuming a 1 micrometer opening.

Pisano et al. disclose a tip which originates from a nearly infinitesimal point" (column 3, lines 66-67,column 4, line 1). Lin et al.'s microneedle tip is etched to remove any single-crystal silicon 5 from the tip end (column 7, lines 42-47) to form a sharp, thin, fragile point less than 12

micrometers thick. Applicants submit that none of the references or any combination thereof teaches or suggests a silicon microprobe with a tip thickness of greater than about 50 micrometers or 100 micrometers as set forth in Claims 64-65. Furthermore, the applicants submit that it would not be obvious to modify Frazier to form a body portion that is thicker than the shaft portion of the microprobe for the reasons set forth above.

Claim 67

Claim 67 adds the limitation of a biosensor integrated into the microprobe device of claim 11. Claim 67 is believed to be allowable due to its dependence from claim 11.

The applicants submit that the rejections of:

claims 9, 13-15, 18 and 20-24 over Frazier et al. in view Pisano et al., as applied to claims 1-8,10,12,25-27,31,34,36-37, 50 and 60 further in view of Say et al.,

claims 9 and 13-15 under 35 U.S.C. 103(a) over Frazier et al. in view of Say et al.,

claims 16 and 17 Frazier et al. in view of Pisano et al. and Say et al further in view of Meade et al., and

the rejection of claim 20 over Frazier et al. in view of Pisano et al. and Say et al, as applied to claims 9, 13-15, 18, 19 and 21-24, in further view of Lin et al.,

are overcome by virtue of their dependence on claims that are believed to be allowable for the reasons discussed above

CONCLUSION

In view of the foregoing, applicants believe that all of the claims are now in condition for allowance. The applicants therefore respectfully request reconsideration of the application and a notice of allowance. If for any reason the Examiner believes any of the claims are not in condition for allowance, he is encouraged to phone Joshua D. Isenberg (Reg. No. 41,088) at (650) 849-7777 so that any remaining issues may be resolved.

Respectfully submitted,

Date: December 21, 2005 Margaret M. Smart

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